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EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 01/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/417,226	SUNDREHAGEN ET AL	
	Examiner	Art Unit	
	Ja-Na Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 3, 2003 has been entered.

Amendment Entry

2. The amendment filed October 3, 2003 was entered. Claims 1-53 have been cancelled. Claims 54-73 have been newly added. Claims 54-73 are under consideration in this office action.

Withdrawal of Rejections

3. The following rejections have been withdrawn in view of applicant's amendments and arguments:

a) The new matter rejection of claims 1, 3-7, 9-12, 16-20, 24-33, 35-36, 42-44 and 47-53 under 35 U.S.C. 112, first paragraph;

b) The rejection of claims 1, 5, 7, 9, 11, 12, 42-44, 47, 48 and 53 under 35 U.S.C. 102(b) as being anticipated by Herbert et al., US Patent 4,680,273;

c) The rejection of claims of claims 3,16,17, 24-26 and 35-36 under 35 U.S.C. 103(a) as being unpatentable over Herbert et al., US Patent 4,680,273 in view of Houts et al., US Patent 4,465,775;

d) The rejection of claims 6-7, 12, and 8-20 under 35 U.S.C. 103(a) as being unpatentable over Herbert et al., and Houts as applied to claims 1,5 and 16 above further in view of McLean et al;

e) The rejection of claims 4 and 49 under 35 U.S.C. 103(a) as being unpatentable over Herbert et al., in view of Houts and further in view of Allen et al., (US Patent 5,374,560); and

f) The rejection of claims 27-33 under 35 U.S.C. 103(a) as being unpatentable over Herbert et al., and McLean et al, as applied to claims 1 above further in view of Hoyle et al.

Response to Arguments

4. Applicant's arguments with respect to claims 54-73 have been considered but are moot in view of the new ground(s) of rejection.

New Grounds of Objection and Rejection

Claim Objections

5. Claim 73 is objected to because of the following informalities: Claim 73 fails to include a period. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 73 is drawn to a kit comprising an immobilized or immobilizable specific binding ligand for TC II or holo-TC II, a plurality of holo-TC II solutions of known concentrations; a release agent and optionally a labeled ligand.

However only anti-TC II antibodies are enabled by the specification and specific binding ligands such as polypeptides, oligopeptide, small organic chemical, binders from combinatorial chemistry libraries or phage display library or specifically binding

sequences of DNA and RNA have not been described as being capable of determining holo-TC II in the manner claimed by claim 54.

The specification does not teach making specific binding ligands such as like polypeptide, oligopeptide, small organic chemical, binders from combinatorial chemistry libraries or phage display library or specifically binding sequences of DNA and RNA that only bind to TC II For instance, there is no disclosure of peptides, small organic chemicals or sequences that preferentially bind TC II. Absent factual evidence that the recited ligands will bind TC II; it is not deemed reasonable that one skilled in the art would know how the claimed ligands would bind to TC II in view of the specification lack of written description. Moreover, the specification recites a range of binding ligands without any specificity to TCII. When the suspension is used for targeting selected cells or tissues the microdevices should contain molecules effective to bind the markers carried on the surface of the target cells (page 8 para. 3). It is known that monoclonal antibodies and associated antibody fragments directed to epitopes on TCII can act as specific binding ligands. However, there is no evidence that the specific binding ligands such as polypeptides, oligopeptide, small organic chemical, binders from combinatorial chemistry libraries or phage display library or specifically binding sequences of DNA and RNA without any specific binding regions specific to TC II have been identified and further, will perform in the assay. Thus, the specification fails to adequately describe such binding ligands. Therefore the recitation of a specific binding ligand without specific regions or sequences directed specifically to TCII will result in an unpredictable use and therefore unreliable correspondence between the broadly claimed specific

binding ligands and the indicated anti-TC II antibodies disclosed in the specification with known specific binding affinity to TCIL; therefore the claimed specific binding ligands lack support regarding utility and/or enablement.

Absent clear demonstration of the production of specific binding ligands such as polypeptides, oligopeptide, small organic chemical, binders from combinatorial chemistry libraries or phage display library or specifically binding sequences of DNA and RNA which specifically and preferentially bind TC II, the recited specific binding ligands could not be used in any manner for the determination of holo-TC II in a body sample comprising the recited steps. In absence of further guidance from Applicants, it is clear that applicants were not in possession of the specific binding ligands which are not monoclonal antibodies.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, make clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). The specification only discloses antibodies as being appropriate binding ligands and there is no disclosure of any other specific binding ligands. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method for determining sequence identity. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential

method of expression. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Thus a skilled artisan cannot envision all the contemplated specific binding ligands and therefore conception cannot be achieved until reduction to practice has occurred. Furthermore, *In The Reagents of the University of California v. Eli Lilly*, (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids does not provide an adequate written description of the genus. Applicants are not required to disclose every species encompassed by a genus, thus the description of a genus is achieved by the recitation of a representative number species, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a nucleic acid molecule...'requires a precise definition, such as by structure, formula, chemical name, or physical properties'".

Therefore, the claims lack written description of the specific binding ligands. In view of the lack of written description of the claims and the lack of written description, the full breadth of the claims fail to meet the written description provision of 35 USC 112, first paragraph.

7. Claims 54-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 54 is vague and indefinite.
Are the terms referring to body sample, initial sample, and body fluid the same as the cell free sample? If so, consistent terminology should be used throughout the claims.

Claim 54 recites contacting the cell free sample with an immobilized or immobilizable specific binding antibody, however the claim language fails to recite what the immobilized or immobilizable specific binding antibody is specific for; for instance is the antibody specific for holo-TC II.

It is also unclear if the alternatively recited antibody fragment for transcobalamin II (TC II) having the recited affinity constant and cross reactivity describes only the qualities of the antibody fragment or if the affinity constant and cross reactivity constant are intended to describe the immobilized or immobilizable specific binding antibody. It is noted that the current claim language does not limit the immobilized or immobilizable specific binding antibody to having the affinity constant and cross reactivity constant.

It is unclear what the ligand is that is being separated? Is the ligand holo-TC II, if so consistent terminology should be used throughout the claims.

It is unclear how the dissociation being so affected that he concentration of the released cobalamin is at least 3 times greater than the concentration of holo-TC II in the initial sample. It is unclear how the released cobalamin amount is affected such that the concentration is at least 3 times greater than the concentration of the holo-TC II in the initial sample. Moreover, it is unclear when the concentration of the initial sample was determined such that it can be compared. Thus, the claim needs to recite all the necessary method steps required to perform the claimed method. Claims 66 and 67 have the same problem and should be appropriately addressed.

Applicants' asserts that the amount of cobalamin bound by the ligand can be determined by a simple experiment. However neither the claims nor the specification

recite steps for the experiment which ascertains the amount of cobalamin. This step must be positive method steps for obtaining at least 80% of TC II present within said cell free sample contained within said ligand bound fraction. Therefore, applicants' assertion is not sufficient to overcome the rejection, in view of applicants' failure to specifically recite the necessary method steps required to perform the instantly claimed method.

8. In claim 56 it is unclear how the "assay is effected to analysis by an automated process." What exact step is being effected to analysis by an automated process? Thus the metes and bound of the claim are unclear and clarification is required to overcome the rejection.

9. Claim 57 recites the limitation " said specific binding ligand " in the claim. There is insufficient antecedent basis for this limitation in the claim.

10. Claim 59 recites the limitation " the isolated cobalamin" in the claim. There is insufficient antecedent basis for this limitation in the claim. Also, the claim refers to "the sample" however it is unclear which sample is being referred too, is it the body sample, the cell free sample, the initial sample or another sample. Clarification is required to overcome the rejection.

11. Claim 60 is vague and indefinite. The claim refers to "said specific binding ligand" in the last lines of the claim, however it is unclear what the "said specific binding ligand" is specific for. It is unclear if the claim is referring to the specific binding ligand for haptocorrin, TC II or something else. Clarification is required to overcome the rejection.

12. Claim 64 recites that the degree of cross-reactivity is between 0.1% and 1% while claim 65 requires that the degree of cross-reactivity is less than 0.1%. However, there is insufficient antecedent basis for this limitation in the claim.

13. Claim 73 is vague and indefinite. Claim 73 recites a kit for use in a diagnostic assay according to claim 54, however the preamble of claim 54 is drawn to an assay method foe determination. There is insufficient antecedent basis for this limitation in the claim. Also, claim 73 is unclear because it refers to an optionally labeled ligand; however it is unclear what the optionally labeled ligand is? Is the ligand holo-TC II, cobalamin or something else? Clarification is required to overcome the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claim 73 is rejected under 35 U.S.C. 102(b) as being anticipated by Herbert et al., US Patent 4,680,273. Herbert et al., teach a method of selectively freeing from transcobalamin II (TCII) and determining the amount vitamin B_{12} or cobalamin in a sample. A decrease in Holo transcobalamin II may be ascertained by comparison with a "normal range" for holo TCII levels (col. 2 lines 39-42). The cobalamin which is carried by TCII may be determined by providing a blood sample which contains essentially only TCII that has been separated from other serum proteins and determining the cobalamin content (col. 3 lines 3-6). Separation steps taught include precipitation of TCII, although other methods for separating TCII from a sample are applicable (col. 3 lines 40-46). TCII can be separated from a sample using selective antibodies (col. 3 lines 54-55) where the antibody can be coupled to a solid support to more easily separate TCII (col. 3 lines 63-64). Once the solution is obtained, the resulting solution may be subjected an assay for cobalamin where a radioassay for cobalamin includes the removal of cobalamin from TCII complex, for example by heating or the use of hydrochloric acid at pH=2 to destroy the TCII and removal of the cobalamin (col. 4 lines 15-20). Cobalamin dissociates from TCII when both the ionic strength and pH are low (col. 4 lines 35-37).

Therefore, Herbert et al., teach a kit for use in a diagnostic assay comprising the same components as those instantly claimed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 703-308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ja-Na Hines
January 13, 2004

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